Allen v. Martin Surfacing

Daubert Hearing

Plaintiff's Presentation

Beginning January 7, 2008

Richard Clapp

Qualifications

Clapp Qualifications

- Education
- Academic Posts
- Professional experience
- Textbooks and Papers
- Federal Judiciary

Assessing Causality: A causes B

- "Direct Proof"?
- Tools:
  - Epidemiology
  - Toxicology
  - Case Reports
  - Extrapolations
- Strengths and Weaknesses

Epi Terminology

- Case-Control Study
- Cohort Study
- Retrospective vs. Prospective
- Statistical Significance and P-value
- Odds Ratio
- Relative Risk

Assessing Causality: A hastens B

- Epidemiology
- Neuroscience (toxicology, etc.)
  - Biological Plausibility
  - Mechanism of Action
- Case reports
- Extrapolations
- Totality → Judgment

Marcia Ratner

Qualifications

Neurotoxins, Neurodegenerative Disease and Aging

- Education
- Bob Feldman
- Bench experience
- Clinical experience
- Teaching experience
- Translational Research
- ALS and Toluene?

Peer Review

- Textbooks
- Journals
  - Clinical Trials
  - Case Reports
  - Letters
- Conferences
- Grand Rounds

Published re Toluene

Environmental Health Perspectives Volume 107, Number 5, May 1999

Grand Rounds

Chronic Toxic Encephalopathy in a Painter Exposed to Mixed Solvents

Robert G. Feldman,[1,2] Marcia Hillary Ratner,[1] and Thomas Ptak[3]

[1]Environmental and Occupational Neurology Program, Department of Neurology, Boston University School of Medicine, Boston, MA 02218 USA; [2]Harvard School of Public Health, Boston, MA 02215 USA; [3]Department of Radiology, Boston University School of Medicine, Boston, MA 02218 USA

Abstract

This paper describes symptoms and findings in a 57-year-old painter who had been exposed to various organic solvents for over 30 years. He began to work as a painter at 16 years of age, frequently working in poorly ventilated areas; he used solvents to remove paint from the skin of his arms and hands at the end of each work shift. The patient and his family noticed impaired short-term memory function and changes in affect in his early forties, which progressed until after he stopped working and was thus no longer exposed to paints and solvents. After the patient's exposures had ended, serial neuropsychological testing revealed persistent cognitive deficits without evidence of further progression, and improvement in some domains. Magnetic resonance imaging revealed global and symmetrical volume loss, involving more white than gray matter. The findings in this patient are consistent with chronic toxic encephalopathy and are differentiated from other dementing processes such as Alzheimer's disease, multi-infarct (vascular) dementia, and alcoholic dementia. Previous descriptions in the literature of persistent neurobehavioral effects associated with chronic exposure to organic solvents corroborate the findings in this case. Key words: cerebral atrophy, dementia, magnetic resonance imaging (MRI), neuropsychological, solvents, toluene. Environ Health Perspect 107:417-422 (1999). [Online 8 April 1999]

http://ehpnet1.niehs.nih.gov/docs/1999/107p417-422feldman/abstract.html

Address correspondences to R.G. Feldman, Department of Neurology, Boston University School of Medicine, Room C-314, 715 Albany Street, Boston, MA 02118-2526 USA.

Presented at the Clinical Pathological Correlation Lecture, Harvard School of Public Health, 25 September 1998.

Received 14 December 1998; accepted 21 January 1999.

Harvard Grand Rounds

Critical Facts Assumed

1. Coach Allen was exposed to neurotoxic chemicals including toluene during the refurbishment of a floor at his place of employment.

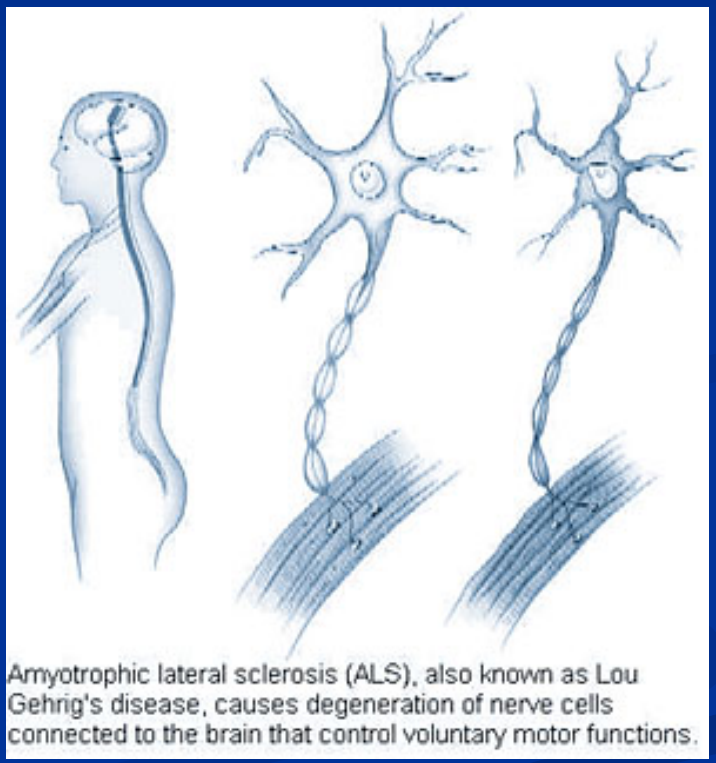
2. Coach Allen experienced acute symptoms consistent with disruption of normal neurological function during his exposure.

3. Coach Allen developed symptoms of ALS in chronological relationship to this specific exposure event.

4. Coach Allen developed and died from ALS much earlier in life than would be expected based on his negative family history.

Personal Evaluation

Amyotrophic Lateral Sclerosis



Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, causes degeneration of nerve cells connected to the brain that control voluntary motor functions.

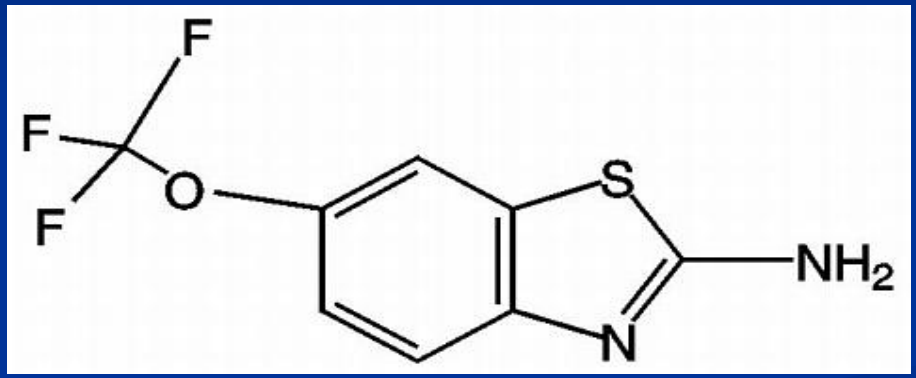
What is ALS?

- Adult-onset neurodegenerative disorder
- Unknown etiology
- Onset is rare before age 40
- Average age at onset of 60 years-old
- Familial cases occur in app. 10% of most case series

Symptoms

- Typically begin in the arms and hands, legs, or swallowing muscles.
- Early symptoms include fasciculations, spasticity, exaggerated reflexes, muscle cramps, and problems with swallowing and forming words.
- Bilateral muscle weakness and atrophy follow as the disease progresses: patients gradually lose strength and the ability to move their arms, legs, and body.
- Speech eventually becomes slurred or nasal.
- In the late stages of the disease muscles of the diaphragm and chest wall fail to function properly and many patients lose the ability to breathe without mechanical ventilation.

Treatment



- Rilutek (riluzole) is a benzothiazole.
- The putative mechanism of action of riluzole is prevention of glutamate mediated excitotoxicity.

If a chemical can be used as a pharmaceutical to extend survival in ALS, can exposure to chemicals also hasten the clinical course?

Representative Example:

Toluene

What is Toluene?

- Toluene (Methylbenzene, Toluol, Phenylmethane) is a volatile organic solvent used in a variety of commercial, industrial and household products, including adhesives, varnishes, lacquers, paints, and thinners.

- The Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) for toluene is 200 parts per million (ppm).

OSHA (1996)

Before a worker is placed in a job with a potential for exposure to toluene, a licensed health care professional should evaluate and document the worker's baseline health status with thorough medical, environmental, and occupational histories, a physical examination, and physiologic and laboratory tests appropriate for the anticipated occupational risks. ***These should concentrate on the function and integrity of the central nervous system*** and skin. Medical monitoring for respiratory disease should be conducted using the principles and methods recommended by NIOSH and the American Thoracic Society.

OSHA cont'd

A preplacement medical evaluation is recommended to assess an individual's suitability for employment at a specific job and ***to detect and assess medical conditions that may be aggravated or may result in increased risk when a worker is exposed to toluene at or below the prescribed exposure limit***. The health care professional should consider the probable frequency, intensity, and duration of exposure as well as the nature and degree of any applicable medical condition. ***Such conditions (which should not be regarded as absolute contraindications to job placement) include a history and other findings consistent with diseases of the central nervous system*** or skin.

Tools to Address General Causation

Epidemiology vs. Neuroscience

Epidemiology

Epidemiological Data

- The "majority" of previous studies have:
  - focused on the etiology of ALS, asking whether chemicals "cause" or "trigger" the disease.
  - not looked at environmental and occupational factors that can influence age at onset of ALS.
  - not stratified subjects by exposure history.
- The only study that evaluated the risk of ALS from exposure to individual, specifically identified, volatile organic compounds found an increase among subjects exposed to alcohols, ketones, benzene, toluene, xylene (*McGuire et al., 1997*).

Neuroscience

Neuroscience & Pharmacology: The Method

- Mechanisms of Drug/Chemical
- Mechanisms of Disease
- Points of Interaction (putative targets)
- In vitro (cellular) studies
- In vivo (animal) studies
- Human data (clinical trials / case reports)

Mechanisms of Action

Mechanism of Action of Toluene

1. Acts on neurotransmitter receptors:
    1. $GABA_A$ receptors
    2. Glutamate receptors
2. Interaction in turn, modulates expression of these receptors
3. These changes in expression directly influence neuronal function, in the presence and absence of Toluene
4. Changes in receptor expression also modulate vulnerability of neurons to influences of other factors

Mechanism of Action of ALS

1. The loss of motor neurons from
    1. Oxidative stress
    2. Glutamate mediated excitotoxicity
2. collectively lead to cell death via apoptosis (programmed cell death).

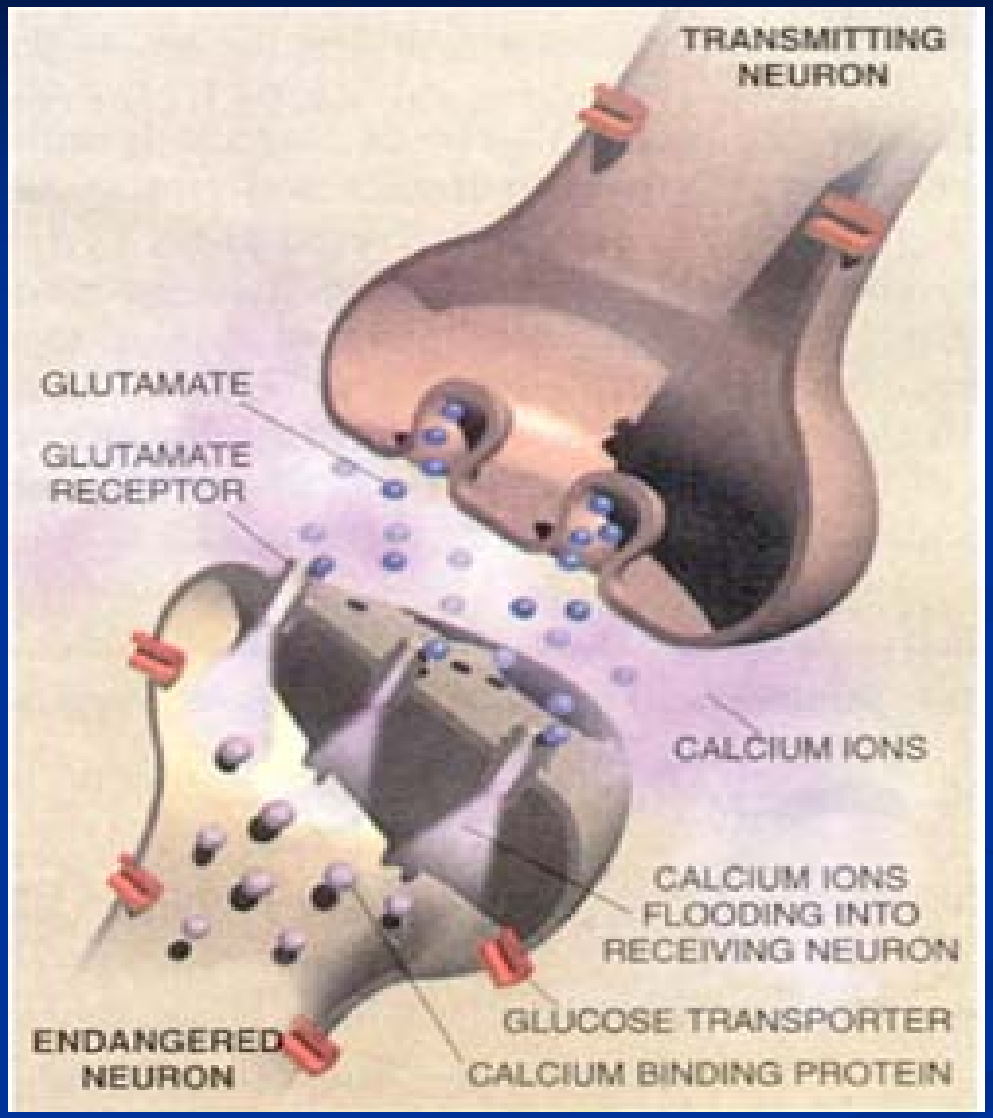
Points of Interaction

Points of Interaction

1. Toluene is a known neurotoxicant.

2. ALS is a known neurodegenerative disorder

3. Studies looking at the mechanism of action of toluene *in vitro* and *in vivo* indicate that it possesses pharmacological and neurotoxicological mechanisms of action that permit it to interact with pathogenic pathways implicated in ALS.


TRANSMITTING NEURON
GLUTAMATE
GLUTAMATE RECEPTOR
CALCIUM IONS
CALCIUM IONS FLOODING INTO RECEIVING NEURON
GLUCOSE TRANSPORTER
CALCIUM BINDING PROTEIN
ENDANGERED NEURON

In Vitro and In Vivo Studies

- Mice exposed to 250 ppm toluene via inhalation for four days showed an increase in severity of handling-induced convulsions upon cessation of exposure (*Wiley et al., 2003*).

- Depletion of glutathione enhances degeneration of motor neurons *in vitro* and *in vivo* (Chi et al., 2007).

Life Sciences

Evaluation of toluene dependence and cross-sensitization to diazepam

Jenny L. Wiley*, Ambuja S. Bale, Robert L. Balster

DEPLETION OF REDUCED GLUTATHIONE ENHANCES MOTOR NEURON DEGENERATION *IN VITRO* AND *IN VIVO*

- To investigate the effects of acute toluene exposure on the amino acid neurotransmitter levels in the hippocampus, an *in vivo* microdialysis study was performed in freely moving mice after a single intraperitoneal administration of toluene (150 and 300 mg/kg).

- The extracellular levels of glutamate and taurine were rapidly and reversibly increased within 30 min after the toluene administration in a dose-dependent manner and returned to the basal level by 1h.

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Toxicology Letters

Toluene induces rapid and reversible rise of hippocampal glutamate and taurine neurotransmitter levels in mice

Tin-Tin Win-Shwe [a,*], D. Mitsushima [b], D. Nakajima [c], S. Ahmed [a], S. Yamamoto [c], S. Tsukahara [c], M. Kakeyama [a], S. Goto [c], H. Fujimaki [c]

Abstract

1. Introduction

Win-Shwe (2007)

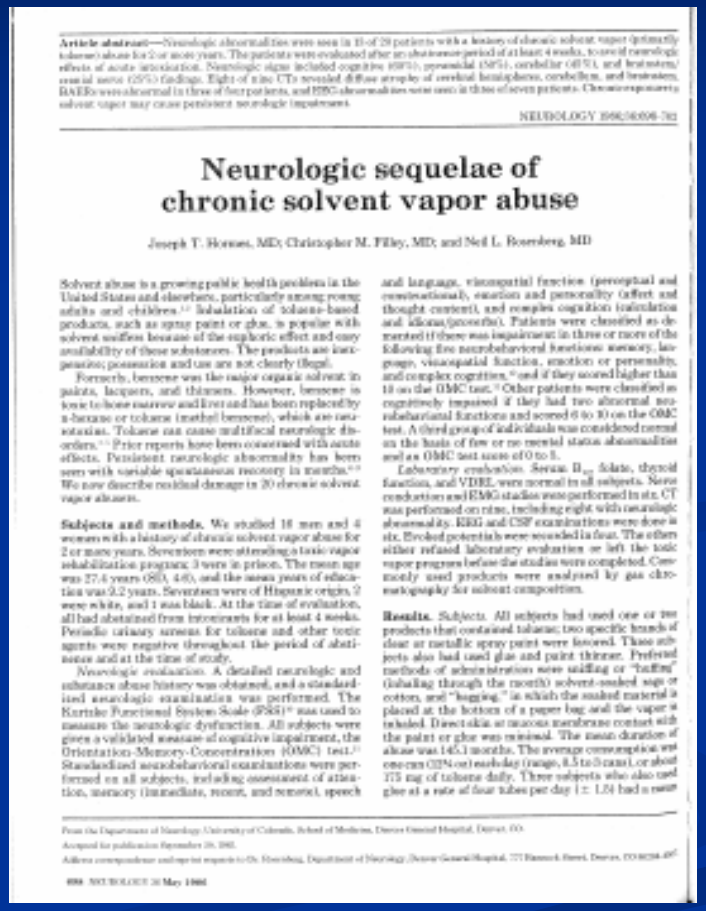
Human Data

Extrapolation:

Why?
How?
When?

- Changes in receptor expression can predipopse the individual to seizures and to excitotoxicity upon cessation of exposure (*Hormes et al., 1986*).

- EEG abnormalities were seen at 4 weeks after cessation of exposure in three of seven patients exposed to toluene (*Hormes et al., 1986*).



Neurologic sequelae of chronic solvent vapor abuse

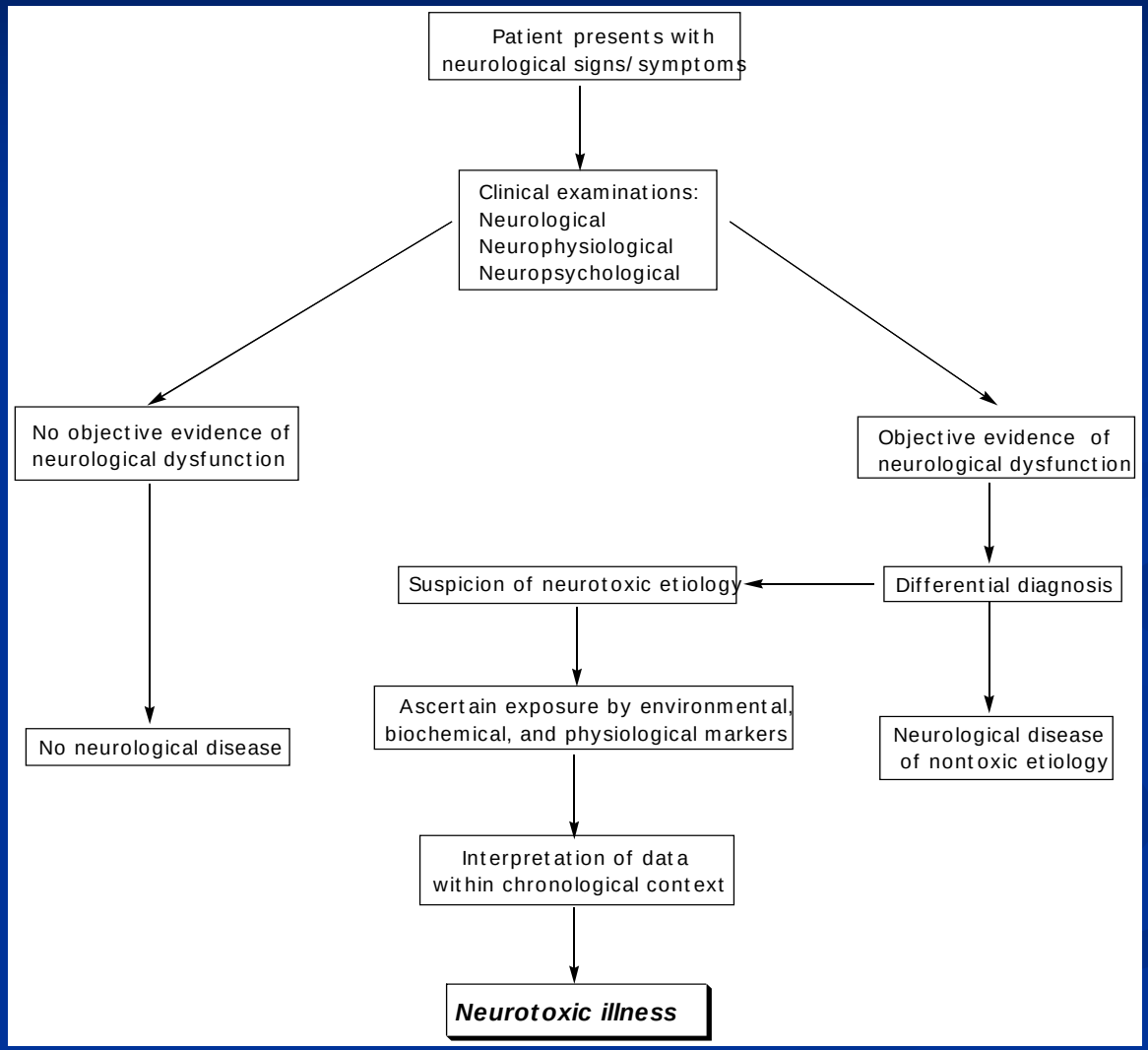
Joseph T. Hormes, MD; Christopher M. Filley, MD; and Neil L. Rosenberg, MD

Conclusion
Toluene hastens early onset of ALS

- Mechanisms of Drug/Chemical 
- Mechanisms of Disease 
- Points of Interaction (putative targets) 
- In vitro (cellular) studies 
- In vivo (animal) studies 
- Human data 

Case-Specific Causation

Peer-reviewed algorithm



Closing

Plaintiffs' Closing

1. Causation vs Hastening
2. Epidemiology vs Neuroscience
3. Basic Neuroscience!
4. Level of Exposure proved via biological effects
5. Differential Diagnosis

Christine Oliver, MD, MPH, MS, FACPM

Qualifications

- Board Certifications
- Graduate Education
- Clinical Practice
- Appointments
- Research
- Misc Honors/Awards

Bases For Opinions

Amyotrophic Lateral Sclerosis (ALS)

- Degenerative Disease Of Neurological System Affecting Upper And Lower Motor Neurons
- 5 - 10% Familial
  - Autosomal Dominant
- 90 - 95% "Sporadic"
  - W/O Demonstrable Cause

ALS: Pathogenesis

- Excess Of Free Radicals Due To:
  - Oxidative Stress
  - Glutamatergic Excitotoxicity
  - Deficiency Cu/Zn Superoxide Dismutase Enzymatic Activity > Increased Glutamate Concentrations Extracellular Space
  - Glutathione Depletion

ALS: Pathogenesis

- Extrinsic toxic Exposures That Contribute To Death Of Motor Neurons Through
  - *Oxidative Stress*
  - *Glutathione Depletion And*
  - *Other Mechanisms That Contribute To Excess Free Radicals*
- Genetic Predisposition Combined With Extrinsic Toxic Exposure That Alters The Course Of The Disease
  - E.G., Cigarette Smoke And Lung Cancer; Aeroallergens And Hayfever)

Daniel L. Allen
DOB 12/07/55, DOD 05/16/04

- **ALS: Chronology**
  - May, 2001: Healthy
  - Late May/Early June: "Overcome With The Fumes": Headache, Nausea, Dizziness, Disorientation
  - Late July: Trip To Aruba – Diarrhea
  - **August 3, 2001** Appt. Dr. Palken
    - C/O Diarrhea, Headache, Dizziness, Diaphoresis
  - **August 29, September 18, October 22, October 23, 2001:**
    - Contact W Dr. Palken's Office C/O Persistent Headache, Dizziness, Nausea

Daniel L. Allen: ALS Chronology (Cont'd)

- **September, 2001:**
  - *Muscle Fasciculations* In Legs
- **October 30, 2001:**
  - Brain MRI/MRA, "WNL"
- **Fall 2001:**
  - *Muscle Fasciculations* Spread To Arms, Upper Body
- **November, 2001:**
  - Dr. Pollen Of HA Clinic UMMC Dx "Transform Migraine" HA
- **January 22, 2002:**
  - Appt Dr. Russell, Lahey C/O *Fasciculations*, Fatigue. Neg FH MND *Elevated CPK*, Abn'l Neurologic Exam w/*Left Foot Drop*
- EMG: "Widespread Fasciculations and Findings of Chronic Denervation And Reinervation"

Daniel L. Allen: ALS Chronology (Cont'd)

- **January 28, 2002**: Appt Dr. Chad, UMMC.
  - Pe > *Fasciculations* Widespread, *Abn'l Neurologic*, *EMG* All C/W Motor Neuron Disease (MND)
- Lumbar Puncture Normal
- Lyme Titer, 24-hr Urine Heavy Metals Negative
- **February, 2002**: Dr. Russell
  - Dx Probable MND. TSH Mildly Elevated
- **March, 2002**:
  - Reactive Depression

Daniel L. Allen: ALS Chronology (Cont'd)

- **August, 2002**: Dr. Palken
  - PE>palpable, Visible Fasciculations, Clonus – Assessment *ALS*
- **October, 2002**:
  - Spirometry WNL
- **Spring, 2003**:
  - Wheelchair Bound
- **Spring, 2003**:
  - Referred Dr. Smyrnios W/Dyspnea; PE>contracted Fingers, Inability To Move Arms, Legs
- **January, 2004**:
  - Spirometry > Marked Decrease FEV_1, FVC
  - Bipap, Cough In-exsufflator Rx

Daniel L. Allen: ALS Chronology (Cont'd)

- **April 13, 2004**:
  - Exam BU By Drs. Jabre And Ratner >Atrophy & Fasciculations Tongue
- **April 21, 2004**:
  - Dr. Smyrnios W/Trouble Swallowing, Eating, Drinking
- **May 4, 2004**:
  - Admit UMMC For Hydration, PEG; Resp Failure (ABG results)
- May 7, 2004: Discharged To Home
- May 16, 2004: Expired

INSTALLATION OF VERSATURF '360' AT HOLY CROSS

- **May 21-June 8, 2001**: 17,000 Sq Ft Flooring In Field House Resurfaced w/Versaturf '360'
- Existing Surface Abraded w/Drum Sander
- Primer *Spray-applied*
- Polyurethane Floor Poured and Allowed to Dry
- Coating *Spray-applied*
- Game Lines Painted

Chemicals Used (MSDS, Ewing Expert Report)

- **Qualitative:**
  - Martin 2164 Urethane Primer (Spray-Applied)

Xylene	35%
Methyl ethyl ketone	45%
Toluene	10%

Chemicals Used

- VERSATURF '360'®
  - Part A:
    - Polyoxy propylene glycol – 65%
      - Fillers and iron oxide – 35%
  - Part B:
    - Di-isocyanates
- POURED ON AND ALLOWED TO DRY

Chemicals Used

- PRIMER:
  - MARTIN AP CONCENTRATE® (SPRAY-APPLIED)
    - Xylene
    - Cellosolve acetate
    - Toluene
    - Ethyl benzene
    - Methyl isobutyl ketone
    - 1-Methoxy-2-propyl acetate

Chemicals Used

- MARTIN SURFACING, INC. S2951 TAN FLAT® urethane coating (SPRAY-APPLIED)
  - Ethyl benzene
  - Methyl isobutyl ketone
  - 1- Methoxy-2-propyl acetate
  - Toluene
  - Xylene
  - Dipropyleneglycol methyletheracetate

Chemicals Used

- **Quantitative** *Emissions* Volatile Materials
  - **Toluene:**
    - 15.7 Lbs. Primer; 3.1-6.9 Lbs 2nd Primer; 73.8 Lbs. Coating
  - **Xylene:**
    - 54.8 Lbs. Primer; 33.6-75.6 Lbs. 2nd Primer; 147.6 Lbs. Coating
  - **MEK:**
    - 70.5 Lbs Primer
  - **MIBK:**
    - 0.6-1.4 Lbs. 2nd Primer; 73.8 Lbs. Coating

Medicial And Scientific Literature:
Cross-sectional Studies

Hawkes et al. The Lancet. 1989:

- **Case-control mortality study of MND deaths among leather workers cf control leather workers. NSD ($p>0.05$) in distribution of tasks. 1981 study MND leather workers found excess (18 MND deaths vs. 9.79 expected, $p<0.00$). 1982 study exposures of shoe factories found toluene, MEK, other solvents. [United Kingdom]**
- **Conclusions: "There is reasonably strong epidemiological evidence to suggest that leather workers are at substantially greater risk of MND…Of several mechanisms, a direct neurotoxic effect deserves most consideration."**

Medicial And Scientific Literature: Cross-sectional Studies (Continued)

- *Chio et al. The Lancet 1989*: Case-control incident study of MND and solvent/glue exposure. 406 patients in clinic cf 406 control pts w neurologic disease other than MND. ORs increased in each of 5 occupations w solvent/glue exp (1.7-5.1), but not SS due to small numbers. For farmers, OR significantly increased (OR 1.72, 95% CI 1.40-2.11) [Italy]

Medicial And Scientific Literature: Cross-sectional Studies (Continued)

- *Gunnarsson et al. Brit J Ind Med 1992:* Case-control study of 92 dx MND patients cf. 372 controls national pop. register. Self-administered questionnaire.
- ORs increased w ALS for **solvents, male, heritability** (**25.1** (3.6-175.8)); w ALS, for **age >61** (**6.8** (3.1-15.1)); w MND 45-59 yrs of age, for **any solvent** (**3.2**), impregnating agents (4.2), pesticides (2.8), petrol (2.5).
- Conclusions: "In our study solvents appeared to be a risk factor for MND especially among those under 60 years of age…..This study … confirmed the results from other studies in so far as some chemical agents appeared as risk factors for MND, especially among genetically predisposed subjects." [Sweden]

Medicial And Scientific Literature: Cross-sectional Studies (Continued)

- *Chancellor et al. J Neuro, Neurosurg, & Psych 1993*: Case-control study to examine risk factors for MND. 103 incident cases ALS +- PBP selected from MND Register cf 103 controls selected from GP patient roster.
- Increased OR for **chemicals/solvents** (**3.3 (1.3-10)**). [Scotland]

Medicial And Scientific Literature: Cross-sectional Studies (Continued)

- ***McGuire et al. Am J Epid 1997:*** Case-control study of incident cases of ALS selected through surveillance system cf. controls selected by random-digit dial or Medicare eligibility list. Focus occupational exposures.
- Structured personal interview: lifetime work hx and exposure to specific chemical agents.
- 4 IHs blinded to dx status used job hx to assess probability and intensity of exposure to metals, solvents, agricultural chemicals

Medicial And Scientific Literature: Cross-sectional Studies (Continued)

- *McGuire et al. 1997*:
- Using expert panel assessment, ORs in males increased for **alcohol, ketones** (**2.6** (1.1-6.1)) and for **agricultural chemicals** (**2.4** (1.2-4.8)); for both genders ORs increased for **alcohol, ketones** (**2.0** (1.0-4.0)); and for **benzene, toluene, or xylene** (**1.7** (0.9-3.0)).
- Using self-report, OR in both genders increased for **solvents** (**2.0**(1.1-3.3)). [US]

Medicial And Scientific Literature: Cross-sectional Studies (Continued)

- *Parks et al. Am J Ind Med 2005*: Study of mortality from neurodegenerative dx using National Occupational Mortality Surveillance System. MND primarily ALS.
- MORs increased w MND for **solvents** (**1.16**(1.01-1.34)), for "oxidative stressors" (1.13(1.01-1.25)), for pesticides (1.86(1.02-3.13)) if age at death <65. [US]

Medicial And Scientific Literature: Cross-sectional Studies (Continued)

- *Morahan et al. Neuroepidemiology 2006:* Case-control study of SALS. 179 cases; 179 matched control. Structured self-administered questionnaires.
- ORs for **solvent**/chemical exposures for group as a whole **1.92**(1.26-2.93), p=0.003; for males, **1.85**(1.12-3.04), p=0.023.
- Comment: "Our study had a significantly increased risk of SALS with occupational exposure to solvents/chemicals which remained significant after correction for multiple testing." [Australia]

Medicial And Scientific Literature:
Prospective Follow-up Studies:

- ***Mitchell et al. J Neuro Sciences 1995:*** Case-control study of MND. Incident cases selected from hospital pt populations 1989-1993 and followed over that time period.
- Used relative risk (RR) estimates to examine associations with possible MND risk factors.
- RR 2.46 (1.47-4.09) among those with exposure to "fumes and dust".
- Relationship between risk factors and survival time was examined.

Medicial And Scientific Literature:
Prospective Follow-up Studies: (Cont'd)

- *Mitchell et al. 1995*
- Exposure to fumes/dust did not significantly impact survival time (p=0.8).
- *Survival Time:*
  - **Age*** was significantly ***inversely*** related to survival time (p<0.001), with an estimated 20% reduction in survival time for each 10-yr increase in age at onset.
  - Corollary is that **younger age** at onset is associated with **longer survival** time.

*Age range among males was 50-70 yrs.

Medicial And Scientific Literature:
Prospective Follow-up Studies: (Cont'd)

- *Chio et al. Neurology 2002:* Prospective follow-up study. 221 ALS patients from 26 neuro depts enrolled 1995-1996 and followed to 10/31/00.
- Purpose: To examine factors related to ALS outcome.
- μ Age at onset 62.8 yrs (SD 11.2 yrs)
- μ Age at diagnosis 63.7 yrs (SD11.2 yrs)
- *Survival Analysis* (n=193):

Medicial And Scientific Literature:
Prospective Follow-up Studies: (Cont'd)

- Age at onset significantly and *inversely* related to survival.
  - ≤ 50, hazard ratio (HR) 1.0; 51-60, HR 1.40; 61-70, HR 1.95; ≥ 71, HR 2.72 (p=0.007)
  - Of 6 subjects < 40 yrs of age at onset, all were alive at the end of the 5 year study period. Other variables also related to outcome: FVC, PEG, lower limb progression rate, EEDC category at diagnosis.

Comment: "Age is probably the most consistent factor related to outcome."

Medicial And Scientific Literature: Prospective Follow-up Studies: (Cont'd)

- *Millul et al. Neuroepidemiology 2005*: Prospective follow-up study of 79 cases of ALS enrolled Jan 1- Dec 31, 1998 and followed through Dec 31, 2002.
- μ Age at onset 67.5 yrs bulbar onset, 63.0 yrs spinal
- μ Age at dx 64.4 yrs

Medicial And Scientific Literature: Prospective Follow-up Studies: (Cont'd)

- *Millul et al. 2005:* Survival time *inversely* related to age at onset:
  - **Age < 55 yrs**, median survival from onset **52.1 mos;** from diagnosis 35.1 mos
  - Age 55-74, median survival from onset 48.5 mos
  - Age ≥ 75, median survival from onset 16.4 mos p<0.0005)

Mr. Allen's Clinical Course

- Age At Onset: 45 Years
- Survival From Onset: 32 Months (Vs. 52.1 Months [Millul])
- Survival From Diagnosis: 27 Months (Vs. 35.1 Months [Millul])

Medical And Scientific Literature: Summary

- **CASE-CONTROL STUDIES:**
- **Two** raise question of link between **solvent** exposure and **MND** (Hawkes, Chio, 1989)
- **Four** show **ORs** close to (Morahan, 2006) or **>2** for exposure to **solvents/chemicals** among **MND/ALS** cases (Gunnarsson, 1992; Chancellor, 1993; McGuire, 1997)
- **One** shows **OR 2.46** for exposure to **"fumes/dust"** (Mitchell, 1995)

Medical And Scientific Literature: Summary

- **MORTALITY STUDY OF MND** (Parkes, 2005):
- Shows MORs < 2 but statistically significantly increased for exposure to solvents and oxidative stressors (1.16 (95% CI 1.01-1.34), 1.13 (95% CI 1.01-1.25), respectively).

Medical And Scientific Literature: Summary

- **PROSPECTIVE FOLLOW-UP STUDIES:**
- Three showed that age is a major predictor of rate of progression of disease and survival time, with age being *inversely* related to survival (Mitchell, 1995; Chio, 2002; Millul, 2005).
- Younger age defined as $\leq$ 50 (Chio) and < 55 (Millul) *significantly* associated with longer survival.

Medical And Scientific Literature: Summary

- LITERATURE DEMONSTRATES
- ***Consistency*** of findings of significant associations between solvent exposures and MND (ALS);
- ***Consistency*** of findings with regard to magnitude of the increase in risk (ORs 2-3+);
- ***Consistency*** of findings across countries, across scientific investigators, and over time.

Key Tenets Of Occupational Medicine

- Occupational exposure can reasonably be expected to be associated with disease outcome **qualitatively**. (*Biologic Plausibility*)
- Occupational exposure can reasonably be expected to be associated with disease outcome **quantitatively**. (*Biologic Plausibility*)
- Occupational exposure is **temporally associated with disease outcome.** (*Temporality*)

Tenets Of Occupational Medicine

- **OTHER FACTORS TO CONSIDER:**
- Occurrence of similar illness or disease among co-workers similarly exposed
- Adequacy of ventilation (local exhaust, general) or isolation of operation
- Use of personal protection (respirators, gloves, impermeable clothing)
- Other possible causes of outcome in question (differential diagnosis)

Differential Diagnosis

- DIFFERENTIAL DIAGNOSIS IS A CORNERSTONE OF ALL MEDICAL SPECIALTIES
  - Patient presents with symptoms and differential diagnosis includes diseases that may cause those symptoms.
  - Occupational medicine is unique in that differential diagnosis *includes* as a *sine qua non* occupational risk factors for the disease.

OPINIONS

- *Mr. Allen had ALS and died as a result of his disease.*
- *Mr. Allen had sporadic ALS.*
- *Time of onset and rate of progression of ALS in Mr. Allen's case were causally related to his exposure to solvent vapors and aerosols during the course of the installation of the Versaturf '360' flooring system in the Field House of The College of the Holy Cross in May/June, 2001.*

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO MR. ALLEN

- His occupational exposure to solvents in 2001 can reasonably be expected on a ***qualitative*** basis to be associated with outcome.
- Certain *solvents* are known to be *neurotoxicants*. Among these are toluene, xylene, ketones, and alcohols.
- Neurotoxicologic research has demonstrated *neurotoxic effects of solvents on motor neurons* – notably research of Dr. Ratner.

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO MR. ALLEN

- Neurotoxicological research has demonstrated ***pathophysiologic mechanisms*** for neurotoxic effects of solvents on motor neurons – using toluene as an example.
- Demonstration of these biochemical mechanisms has lead to an understanding of what causes the death of motor neurons, leading to the development of diseases such as ALS.

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO MR. ALLEN

- This neurotoxicological research has also demonstrated ways in which solvents, acting through similar biochemical mechanisms, enhances and accelerates motor neuron death.
- Thus, in Mr. Allen's case, solvent exposure can reasonably be expected to be associated with earlier onset and more rapid progression of his ALS. (*Experimental Evidence*)

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO MR. ALLEN

- His occupational exposure to solvents in 2001 can reasonably be expected on a ***quantitative*** basis to be associated with outcome.
- The current OSHA PELs for toluene, xylene, and MIBK are 100-200 ppm.
- At 600 ppm 8 hrs, headache, dizziness, euphoria, and nausea
- At 800 ppm, sx are increased and muscle fatigue, "nervousness", and insomnia persist.

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO MR. ALLEN

- Mr. Allen's symptoms during the installation of the flooring system (diary) were "..severe headache, nausea with dizziness as well as disorientation."
- These symptoms are consistent with solvent exposures well above the OSHA PEL – perhaps as high as 600-800 ppm.
- Exposures continued for a number of days, for hours at a time.

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO MR. ALLEN

- Thus, evidence indicates that Mr. Allen's solvent exposures were not "low level."
- Evidence indicates that on a quantitative basis, his exposure to solvents, including but not limited to toluene, can reasonably be expected to have been associated with acceleration of his disease process – with earlier onset and more rapid progression.

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO MR. ALLEN

- Mr. Allen's exposure to solvents in the Field House of Holy Cross in May/June, 2001 preceded the onset of his disease in September, 2001 – satisfying **temporal association** criteria.

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO MR. ALLEN

- **Co-Workers** experienced similar symptoms (affidavit testimony):
- Mr. Napolitano: Pounding HA and nausea
- Coach Bradley: Dizziness and HA "throughout the period"
- Coach Bachia: Lightheaded, burning eyes and throat

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO MR. ALLEN

- **Ventilation Was Inadequate**:
- Coach Allen (diary): "…overcome with fumes"
- Mr. Napolitano (affidavit): "The smell just permeated everything……I could tell it was worse where Coach Allen was located."
- Coach Bradley (affidavit): "…I smelled and felt the effect of the fumes from the chemicals…"
- Coach Bachia (affidavit): Smelled and felt "the effect of the fumes…."

APPLICATION OF TENETS OF OCCUPATIONAL MEDICINE TO Mr. ALLEN

- **Personal Protection:**
  - None – importantly no respiratory protection
- **Differential Diagnosis:**
  - Other possible risk factors for early onset of his disease and more rapid progression were considered. Genetic predisposition, a possible if not likely risk factor, could not be ruled out. No risk factors were found, with the possible exception of thyroid disease.

CONCLUSIONS

- In Mr. Allen's Case,
  - Medical History
  - Exposure Information
  - Medical And Scientific Literature
  - Neurotoxicology
  - Symptomatology Of Mr. Allen And Co-workers

CONCLUSIONS

- REVEAL:
  - Strength of association*
  - Temporality
  - Consistency
  - Biologic plausibility
  - Coherence
  - Experimental evidence

(*Sir Austin Bradford Hill, 1965)

CONCLUSIONS

- ***In Mr. Allen's Case, Exposure To Toluene And Other Solvents In The Field House Of The Holy Cross College In May/June, 2001 Was Causally Related To Time Of Onset And Rate Of Progression Of His ALS.***

William M. Ewing, CIH

Technical Director, Compass Environmental

Qualifications

- Board Certified-American Board of Industrial Hygiene (ABIH) Certified Industrial Hygienist 1983; Sub-specialty in Indoor Environmental Quality 1993, AIHA Fellow Member 1995
- BS degree in biology-Washington & Lee Univ.
  - Additional course work in statistics, and technology and science policy.
  - Completed classes in industrial hygiene, toxicology, respiratory protection, indoor air quality, environmental assessments and asbestos control.

Qualifications (cont'd)

- Conducted over 1500 facility surveys for asbestos management and control
- Indoor air quality projects include office settings, hospitals, and studies of off-gassing of volatile compounds from products
- Directed over 50 courses and lectured in over 200 courses, on topics including respiratory protection, PCB's, air pollution, industrial hygiene, and indoor air quality.

Qualifications (cont'd)

- Over 300 field investigations-chemical plants, textile mills, health care facilities, steel mills, manufacturing plants
- Consultant to Centers for Disease Control, U.S. Public Health Service, Georgia Building Authority
- Past monitoring projects have included spray painting and floor coating worksites

Sources of data

- Affidavits of co-workers and applicator
- Video of field house
- Scott Merrill Deposition
- Rod Paul Deposition
- Technician's Manual-Versaturf "360" installation
- Technical data, diagrams for Graco Sprayers
- Material Safety Data Sheets
- NOAA climatological data
- Floor plans and mechanical plans for field house

Sources of Data (cont'd)

- Expert Report of Marcia Ratner, Ph.D.
- Lord Chemical Products application guidelines
- Martin Surfacing product information
- Martin Surfacing Pre-Installation Checklist
- Dan Allen, personal medical history
- Plaintiff's Answers to Interrogatories

Industrial Hygiene

The field devoted to the

- Identification
- Evaluation
- Control

of hazards in the workplace

Pathways of Exposure

- Via 1st floor offices
  - Air returned to air handler mixing box, then sent to three office areas
- Leakage into return air duct
- Leakage from space to space

Additive Effect of Hazardous Substances (ACGIH)

When two or more hazardous substances have a similar effect on the same target organ or system, their *combined* effect, rather than individual, should be given primary consideration.

Chemicals Used

- **Quantitative** *Emissions* Volatile Materials
  - **Toluene:**
    - 15.7 Lbs. Primer; 3.1-6.9 Lbs 2nd Primer; 73.8 Lbs. Coating. Total 92.6-96.4 Lbs
  - **Xylene:**
    - 54.8 Lbs. Primer; 33.6-75.6 Lbs. 2nd Primer; 147.6 Lbs. Coating. Total 236-278 Lbs
  - **MEK:**
    - 70.5 Lbs Primer
  - **MIBK:**
    - 0.6-1.4 Lbs. 2nd Primer; 73.8 Lbs. Coating

Material Safety Data Sheets

In the event of a spill of product, a self-contained breathing apparatus (SCBA) should be used for clean-up.

(SCBA rated at protection factor of 10,000)

OSHA Requirements

Martin Surfacing was required to conduct personal and area air sampling during field house project, unless they had already accumulated a large quantity of data from many substantially similar projects

Exposure Limits

	PEL (OSHA)	TLV (ACGIH)
Toluene	200 ppm	20 ppm
MIBK	100 ppm	50 ppm
Xylene	100 ppm	100 ppm
Ethyl benzene	100 ppm	100 ppm